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# A new enantiodivergent synthesis of the Geissman–Waiss lactone

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**Abstract**—Intramolecular Michael reaction of methyl (*R*)-6-(*tert*-butoxycarbonylamino)oxy-4-hydroxy-2-hexenoate, in turn obtained from *tert*-butyl (*R*)-3-hydroxy-4-pentenoate, paved the way to the synthesis of both enantiomers of 2-oxa-6-azabicyclo[3.3.0]octan-3-one (the Geissman–Waiss lactone), a precursor for necine bases. Key intermediates in this approach were represented by enantiomeric bicyclic lactones incorporating a [1,2]-oxazinane nucleus, which has been conveniently used to install the pyrrolidine framework of the target compounds through a synthetic scheme featuring the reduction of the nitrogen–oxygen bond and an intramolecular $S_N2$ reaction.


## 1. Introduction

(+)- and (−)-Geissman–Waiss lactones **1**[1] have emerged as key intermediates in the synthesis of a number of pyrrolizidine alkaloids, including the necine bases (+)-retronecine **2** and (−)-platynecine **3**,[2] which possess a wide range of biological activities, such as carcinogenic, antitumor, antispasmodic, hypotensive, and anti-inflammatory (Fig. 1).[3]

The biological importance of this group of compounds has evoked a widespread interest in the development of new methodologies for the enantioselective synthesis of bicyclic lactone **1**.

This compound has been obtained in optically pure form by several groups, taking advantage of classical chiral sources,

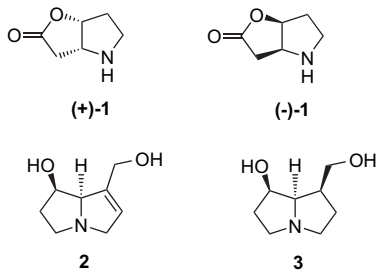


**Figure 1**.

namely *trans*-4-hydroxy-L-proline,[4] *cis*-(2*R*,3*S*)-3-hydroxyproline,[5] D-ribose,[6] D-erythrose,[6,7] L-diethyl tartrate,[8] L-malic acid,[8,9] and (*S*)-pyroglutamic acid.[10] Alternatively, chiral urethanes,[11] 1,4:3,6-dianhydrohexitols,[12] enantiomerically pure 2,5-dihydropyrroles,[13] chiral oxazolidinones,[14] enecarbamates bearing a chiral auxiliary,[15] and a protected (*S*)-maleimide[16] served as versatile building blocks to achieve the chirospecific synthesis of Geissman–Waiss lactone.

Moreover, a number of methods have been developed to prepare *N*-protected derivatives of **1** as suitable starting materials for the synthesis of necine-based alkaloids.[17]

As a continuation of our interest in devising convenient synthetic entries to polyfunctionalized heterocyclic systems, we wish to report in this paper a new simple approach to both (+)- and (−)-Geissman–Waiss lactones **1**.

## 2. Results and discussion

Central to our plan was the use of a chiral bicyclic lactone **7** as the key intermediate (Scheme 1). This compound would represent a convenient precursor of the target compounds, since cleavage of the [1,2]-oxazinane nitrogen–oxygen bond would unmask an amino alcohol moiety to be consecutively used as the starting substrate for an intramolecular $S_N2$ reaction providing the pyrrolidine framework of **1**.

The crucial step in this scheme would be represented by the intramolecular Michael reaction of a chiral γ-hydroxy α,β-unsaturated ester **8**, endowed with a suitably located aminooxy group acting as the nitrogen-centered nucleophile: to the

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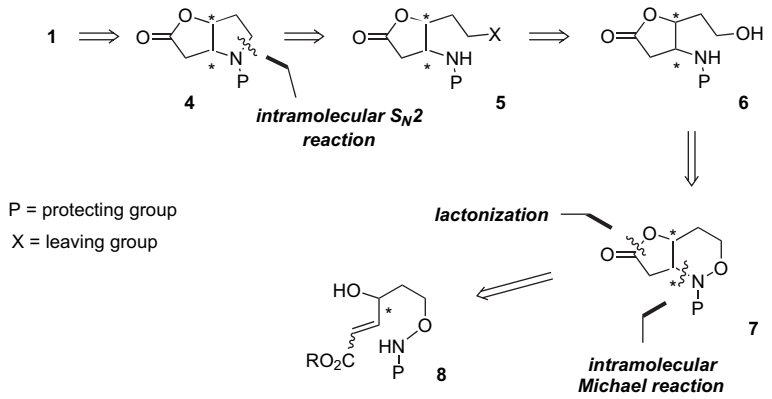
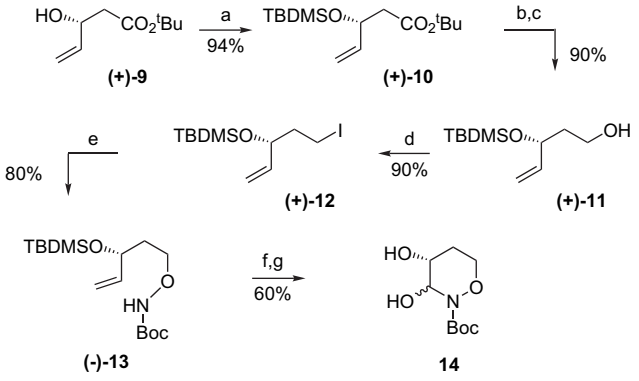



**Scheme 1**.

best of our knowledge, this approach has never been reported in the literature, intramolecular conjugate addition of C-linked nitrogen nucleophiles (e.g., amides and carbamates) to activated olefins being conventionally used to obtain five- or six-membered heterocyclic systems.[8,9a,18]

Having established the essential features of the synthetic project, preparation of a convenient aminooxy derivative to be used in the intramolecular Michael reaction was undertaken.

We reasoned that *tert*-butyl (*R*)-3-hydroxy-4-pentenoate (+)-**9**, in turn obtained by kinetic resolution of the corresponding racemic compound via PS-C lipase (*Pseudomonas cepacia* immobilized on ceramic particles) catalyzed esterification with vinyl acetate,[19] would represent a useful starting chiral source (Scheme 2).




**Scheme 2**. Reagents and conditions: (a) imidazole, TBDMS-Cl, $CH_2Cl_2$, rt, 4 h; (b) DIBALH, toluene, −78 °C, 15 min; (c) $NaBH_4$, MeOH, 0 °C, 10 min; (d) $I_2$, $PPh_3$, imidazole, $Et_2O/CH_3CN/THF$, rt, 15 min; (e) (HO)NHBoc, DBU, $CH_2Cl_2$, rt, 12 h; (f) $O_3$, $CH_2Cl_2$, −78 °C, then $Me_2S$, rt, 12 h; (g) TBAF, THF, rt, 4 h.

Protection of secondary alcohol (+)-**9** as *tert*-butyldimethylsilyl ether (+)-**10**[20] anticipated the conversion of the ester moiety into a hydroxymethyl functionality to be used for the introduction of the aminooxy residue.

Initial attempts to reduce (+)-**10** with lithium aluminum hydride proved unsuccessful, giving a complex mixture in which only traces of the desired reduction product were present.

A different approach was eventually found through a two-step procedure: thus, reduction of the ester group with diisobutylaluminum hydride formed the required aldehyde,[20,21] which was directly treated with sodium borohydride to efficiently provide (+)-**11**[22] in 90% yield over two steps.

Treatment of (+)-**11** with an iodine/triphenylphosphine system, in the presence of imidazole, proceeded smoothly at room temperature to afford the iodide (+)-**12**, which was subsequently treated with *N*-(*tert*-butoxycarbonyl)hydroxylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene[23] to afford the corresponding aminooxy ether (−)-**13**, in 72% overall yield.

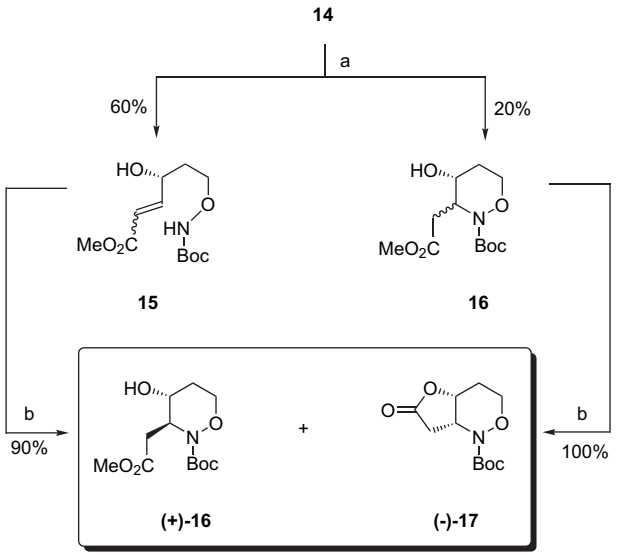
Ozonolysis of the vinyl group, followed by quenching with dimethyl sulfide, and subsequent removal of the silyl protecting group gave the hemiaminal **14** as a mixture of two anomers, as evidenced by its $^1H$ NMR spectrum showing a complete absence of the aldehyde proton and suggesting that the expected α-silyloxyaldehyde had undergone a spontaneous cyclization reaction.

Treatment of the hemiaminal **14** with methyl (triphenylphosphoranylidene)acetate, followed by chromatographic purification of the crude reaction mixture, yielded α,β-unsaturated ester **15** (*Z*:*E*=1:9) and an inseparable 70:30 mixture of diastereomers, which were identified as the cyclized hydroxy ester **16** arising from an intramolecular Michael reaction (Scheme 3).[24]

On treatment of the alkene **15** with tetramethylguanidine, we observed a clean transformation of the starting material into a 70:30 mixture of ester (+)-**16** and lactone (−)-**17**,[24] which could be easily separated by column chromatography. It is likely that the base-induced intramolecular conjugate addition gives rise to an intermediate mixture of *cis*- and *trans*-**16**, the cis-isomer taking part in a smooth lactonization reaction to afford the bicyclic compound.

Similarly, exposure of diastereomers **16** to the same basic treatment resulted in the formation of (−)-**17**, which could be easily separated from unreacted (+)-**16**, thus allowing for a clean separation of *cis*- and *trans*-**16**.

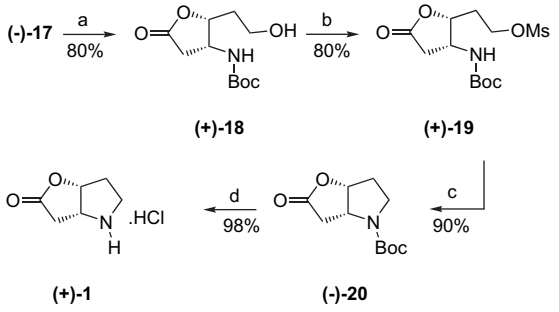
No epimerization at C-4 occurred during the Wittig/intramolecular Michael reaction sequence, as shown by the high




**Scheme 3**. Reagents and conditions: (a) $Ph_3P{=}CH{-}CO_2Me$, toluene, 80 °C, 8 h; (b) TMG, $CH_2Cl_2$, rt, 12 h.

enantiomeric excess of the lactone derivative (−)-**17**, which was estimated to be >98% through chiral gas chromatography performed on a Megadex diethyl *tert*-butylsilyl β-cyclodextrine column.

The stage was now set for us to examine the feasibility of the conversion of (−)-**17** into the Geissman–Waiss lactone. To this end, reductive cleavage of the nitrogen–oxygen bond was the first goal. After extensive experimentation, we found that the reduction could be conveniently achieved by treatment of (−)-**17** with molybdenum hexacarbonyl[25] in wet acetonitrile, leading to the formation of amino alcohol (+)-**18** in 80% yield (Scheme 4).



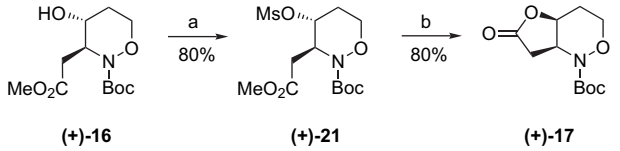

**Scheme 4**. Reagents and conditions: (a) $Mo(CO)_6$, $CH_3CN$, $H_2O$, reflux, 4 h; (b) $CH_3SO_2Cl$, $Et_3N$, $CH_2Cl_2$, 0 °C, 10 min; (c) TMG, $CH_2Cl_2$, rt, 12 h; (d) HCl, $Et_2O$, rt, 8 h.

Mesylation of (+)-**18** with methanesulfonyl chloride/triethylamine system gave rise to (+)-**19**, which underwent the planned intramolecular $S_N2$ reaction by treatment with tetramethylguanidine to afford the known *N*-Boc protected Geissman–Waiss lactone (−)-**20**.[12,14]

Subsequent acidic deprotection gave (+)-**1** as the hydrochloride, whose physical and spectral data were consistent with those reported in the literature.[4b,14,16]

Based on these results, we turned our attention to the synthesis of (−)-Geissman–Waiss lactone, reasoning that the enantiomer of (−)-**17** should represent a convenient precursor to be used in a same synthetic sequence as that reported in Scheme 4.

The most straightforward access to (+)-**17** would be based on the use of ester (+)-**16**, since its functionalities at C-3 and C-4 should be elaborated according to the procedure reported by Shishido et al.[8] for the assemblage of a five membered lactone nucleus condensed with a protected pyrrolidine framework. As the key step in this approach was represented by an intramolecular mesylate displacement promoted by a suitably located carboxylate function, we treated (+)-**16** with methanesulfonyl chloride and triethylamine in the presence of 4-dimethylaminopyridine to obtain the intermediate mesylate (+)-**21** (Scheme 5).




**Scheme 5**. Reagents and conditions: (a) $CH_3SO_2Cl$, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C, 1 h; (b) LiOH, dioxane/$H_2O$, rt, 12 h.

The ester of methanesulfonate (+)-**21** was then hydrolyzed in order to liberate the corresponding carboxylic acid, which was the nucleophile in the subsequent intramolecular $S_N2$ reaction.

Gratifyingly, basic treatment of (+)-**21** took place with concomitant mesylate displacement and inversion of configuration at C-4, allowing us to gain (+)-**17** in a very good yield.

Lactone (+)-**17** was spectroscopically identical to (−)-**17** except for the sign of the optical rotation and thus a route to the formal synthesis of (−)-**1** was established.

## 3. Conclusion

In summary, we have demonstrated that the intramolecular conjugate addition of an aminooxy group to an activated olefin represents a convenient tool for the synthesis of [1,2]-oxazinane derivatives.[26] Reductive cleavage of the nitrogen–oxygen bond allows for a clean conversion of the heterocyclic nucleus to a pyrrolidine framework through intramolecular nucleophilic displacement of a leaving group conveniently introduced in the released amino alcohol.

This approach provided a new entry to both enantiomers of Geissman–Waiss lactone **1** and could be used to prepare optically active precursors of hydroxylated pyrrolidine-based alkaloids.

## 4. Experimental

### 4.1. General

Solvents were distilled prior to use, following standard procedures, and reactions were performed under nitrogen or argon atmosphere, except ozonolysis. Silica gel 60 $F_{254}$

plates were used to monitor synthetic transformations, visualization being done under UV light or using 2% $KMnO_4$ solution. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Chromatographic purifications were carried out using 70–230 mesh silica gel. Melting points were determined on a Büchi–Tottoli apparatus and were uncorrected. Infrared (IR) spectra were recorded with an FTIR PARAGON-100 spectrometer. Nuclear magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) were taken on a Mercury Plus spectrometer at 400 MHz and 100 MHz, respectively. Variable-temperature $^1$H NMR spectra were recorded at 200 MHz with a Varian VXR-200 spectrometer. Chemical shifts ($\delta$ values) are given in parts per million downfield from tetramethylsilane as the internal standard. Optical rotations were measured with a Perkin–Elmer 241 MC Polarimeter. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

The starting *tert*-butyl (*R*)-3-hydroxy-4-pentenoate (+)-**9** and its *tert*-butyldimethylsilyl ether (+)-**10** have been previously described and were characterized by comparison with reported data.[19,20]

**4.1.1. (+)-(*R*)-3-(*tert*-Butyl-dimethylsilyl)oxy-pent-4-en-1-ol (11).** *tert*-Butyldimethylsilyl ether (+)-**10** (1.50 g, 5.23 mmol) was reduced with DIBALH (6.30 mL, 1 M in hexane, 6.30 mmol) according to the protocol described by Tan and Holmes.[20] The obtained crude aldehyde[21] was dissolved in MeOH (20 mL) and the resulting solution cooled at 0 °C. $NaBH_4$ (0.22 g, 5.75 mmol) was added portionwise and the mixture stirred at room temperature for 10 min. Removal of the solvent in vacuo was followed by column chromatography ($Et_2O$/hexanes 2:8) of the residue to furnish (+)-**11** (1.02 g, 90%) as a yellowish oil. $[\alpha]_D^{20}$ +4.0 (*c* 1.17, $CHCl_3$);[27] spectral data were in close agreement with the literature,[22] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.65–1.77 (m, 1H), 1.78–1.92 (m, 1H), 3.66–3.75 (m, 1H), 3.76–3.87 (m, 1H), 4.36–4.45 (m, 1H), 5.10 (dt, *J*=9.6, 1.2 Hz, 1H), 5.22 (dt, *J*=17.2, 1.2 Hz, 1H), 5.85 (ddd, *J*=17.2, 9.6, 5.8 Hz, 2H). Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 61.15; H, 11.02.

**4.1.2. (+)-(*R*)-3-(*tert*-Butyl-dimethylsilyl)oxy-5-iodo-1-pentene (12).** A solution of (+)-**11** (1.00 g, 4.62 mmol) in THF (10 mL) was added dropwise to a cooled (0 °C) solution of $PPh_3$ (1.83 g, 7.00 mmol) and imidazole (0.50 g, 7.40 mmol) in $Et_2O$ (13 mL) and MeCN (7 mL). The mixture was kept at the same temperature for 1 h, then $I_2$ (2.03 g, 8.0 mmol) was added and stirring was continued for 15 min. The reaction mixture was diluted with $Et_2O$ (20 mL) and washed with satd $NaHSO_3$ (20 mL) until colorless. The two phases were separated and the aqueous layer extracted several times with $Et_2O$. The combined organic phases were dried and evaporated to a crude product, which was purified by column chromatography (hexanes) to yield (+)-**12** (1.35 g, 90%) as a colorless oil. $[\alpha]_D^{20}$ +7.5 (*c* 0.75, $CHCl_3$); IR (neat): 2955, 2929, 2894, 2857, 1643, 1471, 1361, 1257, 1089, 926, 835, 776 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.04 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.90–2.07 (m, 2H), 3.10–3.27 (m, 2H), 4.18 (app q, *J*=6.4 Hz, 1H), 5.08 (dt, *J*=10.6, 1.6 Hz, 1H), 5.20 (dt, *J*=17.2, 1.6 Hz, 1H), 5.77 (ddd, *J*=17.2, 10.6, 6.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.6 ($CH_3$), −4.1 ($CH_3$), 2.7 ($CH_2$), 18.2 (C), 25.9 ($3CH_3$), 41.7 ($CH_2$), 73.8 (CH), 114.9 ($CH_2$), 140.5 (CH). Anal. Calcd for $C_{11}H_{23}IOSi$: C, 40.49; H, 7.10. Found: C, 40.36; H, 7.12.

**4.1.3. (−)-(*R*)-3-(*tert*-Butyl-dimethylsilyl)oxy-5-(*tert*-butoxycarbonylamino)oxy-1-pentene (13).** DBU (2.30 mL, 15.5 mmol) was added dropwise to a cooled (0 °C) solution of iodide (+)-**12** (1.00 g, 3.10 mmol) and *N*-(*tert*-butoxycarbonyl)hydroxylamine (2.06 g, 15.5 mmol) in $CH_2Cl_2$ (10 mL). After being stirred for 12 h at room temperature, water was added and the two phases separated. The aqueous layer was washed several times with $CH_2Cl_2$, and the organic fractions were collected, dried, and evaporated. The crude residue was purified by column chromatography ($Et_2O$/hexanes 1:6) to give (−)-**13** (0.82 g, 80%) as a yellowish oil. $[\alpha]_D^{20}$ −4.3 (*c* 1.78, $CHCl_3$); IR (neat): 3287, 2958, 2930, 2857, 1723, 1700, 1367, 1255, 1086, 1017, 835, 775 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.03 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.48 (s, 9H), 1.72–1.92 (m, 2H), 3.92 (t, *J*=6.6 Hz, 2H), 4.22–4.32 (m, 1H), 5.04 (dt, *J*=10.4, 1.2 Hz, 1H), 5.17 (dt, *J*=17.2, 1.2 Hz, 1H), 5.80 (ddd, *J*=17.2, 10.4, 6.0 Hz, 1H), 7.12 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −5.0 ($CH_3$), −4.4 ($CH_3$), 18.2 (C), 25.8 ($3CH_3$), 28.2 ($3CH_3$), 36.2 ($CH_2$), 70.6 (CH), 73.1 ($CH_2$), 81.6 (C), 114.0 ($CH_2$), 114.1 (CH), 156.8 (C). Anal. Calcd for $C_{16}H_{33}NO_4Si$: C, 57.97; H, 10.03; N, 4.22. Found: C, 58.01; H, 10.00; N, 4.23.

**4.1.4. Mixture of (3*R*,4*R*)- and (3*S*,4*R*)-3,4-dihydroxy-[1,2]-oxazinane-2-carboxylic acid *tert*-butyl ester (14).** An ozone-enriched stream of oxygen was bubbled through a −78 °C cold solution of (−)-**13** (1.00 g, 3.02 mmol) in $CH_2Cl_2$ (50 mL) until it turned light blue. Excess ozone was removed by flushing the solution with nitrogen, $Me_2S$ (0.22 mL, 3.02 mmol) was successively added, and the mixture was kept overnight at room temperature. The solvent was removed in vacuo, the residue dissolved in $CH_2Cl_2$, and passed through a short path of silica gel to give a crude product, which was immediately dissolved in THF (20 mL). The resulting solution was cooled at 0 °C, then TBAF (1.90 g, 6.04 mmol) was added portionwise and stirring continued at room temperature for 4 h. The solvent was evaporated and the crude product purified by column chromatography (EtOAc) to furnish the hemiaminal **14** (0.40 g, 60%) as a white amorphous solid. This was an inseparable mixture of anomers in a 60:40 ratio, based on the integrals of the anomeric H-3; IR (neat): 3335, 2963, 1723, 1680, 1258, 1068, 1014, 995, 792 $cm^{-1}$; $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 1.49 (s, 9H), 1.67–1.74 (m, 1H), 2.04–2.16 and 2.26–2.36 (m, 1H), 3.68–3.88 (m, 2H), 4.02–4.10 and 4.18–4.26 (m, 1H), 5.28–5.32 and 5.45–5.48 (m, 1H). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.20; H, 7.84; N, 6.42.

**4.1.5. Wittig reaction of 14.** A suspension of **14** (0.50 g, 2.30 mmol) in toluene (20 mL) was heated at 80 °C for 30 min. Methyl (triphenylphosphoranylidene)acetate (1.15 g, 3.45 mmol) was then added and stirring continued for 8 h. The mixture was concentrated in vacuo, the residue triturated with $Et_2O$, and filtered. Evaporation of the solvent and column chromatography (EtOAc/hexanes 1:1) of the crude product furnished, in order of elution, the unsaturated ester **15** (0.38 g, 60%) as an inseparable *E*/*Z* mixture in a 9:1

ratio, and **16** (0.13 g, 20%) as an inseparable mixture of cis- and trans-isomers in a 1:2 ratio. *Compound **15***: colorless oil; IR (neat): 3500, 3300, 2954, 2930, 2857, 1723, 1660, 1367, 1250, 1164, 1086, 835, 776 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): only the resonances for the *E*-isomer are clearly detectable, $\delta$ 1.47 (s, 9H), 1.63–1.74 (m, 1H), 1.88–2.00 (m, 1H), 3.73 (s, 3H), 3.98–4.10 (m, 2H), 4.60–4.70 (m, 1H), 6.16 (A part of ABX system, *J*=15.6, 2.0 Hz, 1H), 6.95 (B part of ABX system, *J*=15.6, 4.0 Hz, 1H), 7.37 (br s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 28.2 ($3CH_3$), 34.4 ($CH_2$), 51.7 ($CH_3$), 68.3 (CH), 74.0 ($CH_2$), 82.7 (C), 119.7 (CH), 150.0 (CH), 157.7 (C), 174.7 (C). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.20; H, 7.71; N, 5.11. *Compound **16***: colorless oil; IR (neat): 3456, 2978, 1738, 1720, 1695, 1367, 1255, 1161, 1094, 1020, 991 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): major isomer $\delta$ 1.48 (s, 9H), 1.58–1.68 (m, 1H), 2.04–2.18 (m, 1H), 2.62 (A part of ABX system, *J*=16.0, 7.0 Hz, 1H), 2.84 (B part of ABX system, *J*=16.0, 7.0 Hz, 1H), 2.66–2.78 (br s, 1H), 3.67 (s, 3H), 3.79 (app dd, *J*=11.4, 5.6 Hz, 1H), 3.88–3.94 (m, 1H), 4.25–4.36 (m, 1H), 4.54–4.64 (m, 1H); most of the resonances for the minor isomer are superimposed to those of the major isomer, except for the following ones: 1.80–1.95 (m, 2H), 2.75 (d, *J*=6.0 Hz, 2H), 3.84–4.05 (m, 2H), 4.65–4.73 (m, 1H). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.20; H, 7.71; N, 5.11.

**4.1.6. (+)-(3*S*,4*R*)-4-Hydroxy-3-(methoxycarbonyl)-methyl-[1,2]-oxazinane-2-carboxylic acid *tert*-butyl ester (16) and (−)-(1*R*,5*R*)-6-*tert*-butoxycarbonyl-2,7-dioxa-6-azabicyclo[4.3.0]nonan-3-one (17).** A solution of alkene **15** (0.50 g, 1.82 mmol) in $CH_2Cl_2$ (10 mL) was stirred at room temperature for 12 h in the presence of 1,1,3,3-tetramethylguanidine (0.23 mL, 1.82 mmol), then the solvent was evaporated. Column chromatography of the residue (EtOAc/hexanes 1:1) gave (+)-**16** (0.30 g, 60%) and (−)-**17** (0.13 g, 30%). *Compound (+)-**16***: colorless oil. $[\alpha]_D^{20}$ +63.0 (*c* 1.66, $CHCl_3$); IR (neat): 3456, 2978, 1738, 1720, 1695, 1367, 1255, 1161, 1094, 1020, 991 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (s, 9H), 1.58–1.68 (m, 1H), 2.04–2.18 (m, 1H), 2.62 (A part of ABX system, *J*=16.0, 7.0 Hz, 1H), 2.84 (B part of ABX system, *J*=16.0, 7.0 Hz, 1H), 2.66–2.78 (br s, 1H), 3.67 (s, 3H), 3.79 (app dd, *J*=11.4, 5.6 Hz, 1H), 3.88–3.94 (m, 1H), 4.25–4.36 (m, 1H), 4.54–4.64 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 27.1 ($CH_2$), 28.3 ($3CH_3$), 34.2 ($CH_2$), 52.0 ($CH_3$), 57.4 (CH), 64.5 (CH), 65.7 ($CH_2$), 81.9 (C), 155.7 (C), 171.4 (C). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.20; H, 7.71; N, 5.11. *Compound (−)-**17***: white solid, mp 72–73 °C. $[\alpha]_D^{20}$ −135.0 (*c* 1.00, $CHCl_3$); IR (neat): 2975, 1774, 1712, 1689, 1365, 1324, 1305, 1259, 1160, 1081, 1017, 980, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.49 (s, 9H), 2.00–2.20 (m, 2H), 2.80 (d, *J*=6.4 Hz, 2H), 4.00–4.20 (m, 2H), 4.76–4.90 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 25.3 ($CH_2$), 28.2 ($3CH_3$), 32.2 ($CH_2$), 54.2 (CH), 65.9 ($CH_2$), 73.2 (CH), 82.8 (C), 154.6 (C), 174.7 (C). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.40; H, 7.01; N, 5.78.

**4.1.7. (+)-(4*R*,5*R*)-4-(*tert*-Butoxycarbonyl)amino-5-(2-hydroxy)ethyl-dihydrofuran-2-one (18).** A solution of (−)-**17** (0.2 g, 0.82 mmol) in MeCN (12 mL) containing water (0.4 mL) was treated with $Mo(CO)_6$ (0.32 g, 1.23 mmol) and refluxed for 4 h. The cooled mixture was filtered through Celite and the filtrate evaporated. The residue was purified by column chromatography (EtOAc/hexanes 1:1 increasing to EtOAc) to give (+)-**18** (0.16 g, 80%) as a white solid, mp 128–130 °C. $[\alpha]_D^{20}$ +78.0 (*c* 0.86, $CH_3OH$); IR (neat): 3518, 3328, 2978, 1775, 1703, 1685, 1533, 1362, 1256, 1169, 1042, 1006, 939, 806 $cm^{-1}$; $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 1.44 (s, 9H), 1.78–1.92 (m, 2H), 2.39 (A part of ABX system, *J*=18.0, 2.4 Hz, 1H), 3.00 (B part of ABX system, *J*=18.0, 8.0 Hz, 1H), 3.64–3.76 (m, 2H), 4.40–4.46 (m, 1H), 4.70–4.80 (m, 1H); $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ 28.6 ($3CH_3$), 33.5 ($CH_2$), 36.6 ($CH_2$), 51.1 (CH), 59.3 ($CH_2$), 80.5 (C), 82.1 (CH), 157.8 (C), 177.7 (C). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.95; H, 7.70; N, 5.70.

**4.1.8. (+)-(4*R*,5*R*)-4-(*tert*-Butoxycarbonyl)amino-5-[2-(methanesulfonyl)oxy]ethyl-dihydrofuran-2-one (19).** An ice-cooled (0 °C) solution of (+)-**18** (0.21 g, 0.86 mmol) in $CH_2Cl_2$ (10 mL) was treated with $Et_3N$ (0.19 mL, 1.30 mmol) and $MeSO_2Cl$ (0.10 mL, 1.30 mmol), and the mixture stirred at room temperature for 10 min. Brine was added, the organic phase separated, dried, and evaporated. The crude product was purified by column chromatography ($Et_2O$) to give (+)-**19** (0.22 g, 80%) as a white solid, mp 108–110 °C. $[\alpha]_D^{20}$ +124.0 (*c* 1.00, $CHCl_3$); IR (neat): 3356, 2980, 1770, 1680, 1514, 1339, 1248, 1160, 910 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.42 (s, 9H), 2.00–2.20 (m, 2H), 2.46 (A part of ABX system, *J*=18 Hz, 1H), 2.94 (B part of ABX system, *J*=18.0, 8.0 Hz, 1H), 3.03 (s, 3H), 4.30–4.47 (m, 2H), 4.50–4.60 (m, 1H), 4.68 (dt, *J*=9.6, 4.4 Hz, 1H), 5.12 (br d, *J*=8.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 28.3 ($3CH_3$), 29.3 ($CH_2$), 36.3 ($CH_2$), 37.4 ($CH_3$), 49.9 (CH), 66.3 ($CH_2$), 79.6 (CH), 80.6 (C), 155.2 (C), 174.5 (C). Anal. Calcd for $C_{12}H_{21}NO_7S$: C, 44.57; H, 6.55; N, 4.33. Found: C, 44.60; H, 6.52; N, 4.35.

**4.1.9. (−)-(1*R*,5*R*)-6-*tert*-Butoxycarbonyl-2-oxa-6-azabicyclo[3.3.0]octan-3-one (20).** A solution of (+)-**19** (0.15 g, 0.46 mmol) and 1,1,3,3-tetramethylguanidine (64 μL, 0.51 mmol) in $CH_2Cl_2$ (5 mL) was stirred at room temperature for 12 h, then the solvent was evaporated. Column chromatography ($Et_2O$) of the residue gave (−)-**20** (90 mg, 90%) as a white solid, mp 110–111 °C (lit.[12] mp 111–112 °C; lit.[14] mp 111 °C). $[\alpha]_D^{20}$ −150.0 (*c* 0.50, $CHCl_3$) {lit.[12] $[\alpha]_D^{30}$ −141.4 (*c* 0.44, $CHCl_3$); lit.[14] $[\alpha]_D^{27}$ −131.1 (*c* 1.00, $CHCl_3$)}; $^1H$ NMR (200 MHz, $CDCl_3$ at 50 °C): $\delta$ 1.48 (s, 9H), 1.90–2.13 (m, 2H), 2.29 (part of ABX system, *J*=14.0, 6.0 Hz, 1H), 2.70–2.90 (m, 1H), 3.37 (dt, *J*=11.0, 6.0 Hz, 1H), 3.60–3.90 (m, 1H), 4.35–4.50 (m, 1H), 5.05 (app t, *J*=5.0 Hz, 1H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.25; H, 7.51; N, 6.18.

**4.1.10. (+)-(1*R*,5*R*)-2-Oxa-6-azabicyclo[3.3.0]octan-3-one hydrochloride (1·HCl).** Urethane (−)-**20** (0.10 g, 0.44 mmol) was deprotected with HCl as described by Kouyama et al.[14] to furnish (+)-**1**·HCl (70 mg, 98%) as white needles, mp 184–185 °C (lit.[4b] mp 185–186 °C; lit.[8] mp 185–186.5 °C). $[\alpha]_D^{20}$ +48.5 (*c* 0.20, MeOH) {lit.[4b] $[\alpha]_D$ +48.5 (*c* 1.5, MeOH); lit.[8] $[\alpha]_D^{25}$ +48.8 (*c* 0.20, MeOH)}. Spectral data were in good agreement with those reported in the literature,[16] $^1H$ NMR (400 MHz, $D_2O$): $\delta$ 2.20–2.40 (m, 2H), 2.90 (dd, *J*=19.5, 1.4 Hz, 1H), 3.30 (dd, *J*=8.8, 19.5 Hz, 1H), 3.40 (dt, *J*=11.4, 6.6 Hz, 1H), 3.50–3.60 (m,

1H), 4.60–4.80 (m, 1H), 5.42 (br t, $J$=5.0 Hz, 1H). Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.10; H, 6.13; N, 8.58.

**4.1.11. (+)-(3*S*,4*R*)-4-(Methanesulfonyl)oxy-3-(methoxycarbonyl)methyl-[1,2]-oxazinane-2-carboxylic acid *tert*-butyl ester (21).** To an ice-cooled (0 °C) solution of the hydroxy ester (+)-**16** (0.23 g, 0.83 mmol) in $CH_2Cl_2$ (10 mL) were successively added $Et_3N$ (0.18 mL, 1.24 mmol), $MeSO_2Cl$ (0.10 mL, 1.24 mmol), and a catalytic amount of DMAP. After being stirred at room temperature for 1 h, the mixture was diluted with brine and the organic layer separated. The aqueous phase was further extracted with $CH_2Cl_2$, the organic fractions were collected, dried, and evaporated. The crude product was purified by column chromatography (EtOAc/hexanes 1:2) to afford (+)-**21** (0.23 g, 80%) as a colorless oil. $[\alpha]_D^{20}$ +40.1 (*c* 1.00, $CHCl_3$); IR (neat): 2979, 1717, 1355, 1170, 1091, 926, 846 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.51 (s, 9H), 1.90–2.00 (m, 1H), 2.22–2.38 (m, 1H), 2.75 (A part of ABX system, $J$=16.6, 8.8 Hz, 1H), 2.84 (B part of ABX system, $J$=16.6, 6.0 Hz, 1H), 3.13 (s, 3H), 3.71 (s, 3H), 3.90 (app dd, $J$=11.6, 5.6 Hz, 1H), 4.18–4.28 (m, 1H), 4.76–4.82 (m, 1H), 4.85–4.90 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 26.3 ($CH_2$), 28.3 ($3CH_3$), 33.9 ($CH_2$), 38.6 ($CH_3$), 52.3 ($CH_3$), 65.3 ($CH_2$), 73.6 (2CH), 82.4 (C), 154.5 (C), 170.7 (C). Anal. Calcd for $C_{13}H_{23}NO_8S$: C, 44.18; H, 6.56; N, 3.96. Found: C, 44.30; H, 6.54; N, 3.98.

**4.1.12. (+)-(1*S*,5*S*)-6-*tert*-Butoxycarbonyl-2,7-dioxa-6-azabicyclo[4.3.0]nonan-3-one (17).** A solution of (+)-**21** (0.24 g, 0.68 mmol) and $LiOH\cdot H_2O$ (33 mg, 0.78 mmol) in a mixture of dioxane (4 mL) and water (1 mL) was stirred at room temperature for 12 h. The solvent was stripped off, then water and $Et_2O$ were added. The organic layer was separated, the aqueous phase was extracted several times with $Et_2O$, and the combined organic extracts were dried. Evaporation of the solvent gave (+)-**17** (0.13 g, 80%) as a white solid, mp 71–72 °C. $[\alpha]_D^{20}$ +134.0 (*c* 1.00, $CHCl_3$). Spectral data were identical to those of (−)-**17**. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.38; H, 7.02; N, 5.77.

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